Michael J. Kosnett, MD, MPH
Draft NTP Monograph on Health Effects of Low-Level Lead
Public Comments to the Peer Review Committee, November 17, 2011

[These comments reflect my personal views as a medical toxicologist interested in this topic. I am not offering these comments on behalf of any organization or stakeholder.]

I applaud the draft NTP monograph as an important undertaking to collect and analyze the impacts of low level lead exposure on human health. I fully concur with the analysis in multiple places, particularly with respect to the well documented adverse effect of low level lead exposure on neurocognitive development in children. In the brief time available to me this morning, I would like to offer a constructive suggestion regarding the draft document's implicit analysis of the causal relationship between low level lead exposure and a few other endpoints.

Associations between blood lead concentrations less than 10 µg/dL and cardiovascular health endpoints in adults may readily reflect the impact of cumulative lead exposure, including decades of earlier life exposure in which the blood lead concentrations exceeded 10 µg/dL. In most if not all of the studies in which such associations have been demonstrated, a substantial percentage of the subjects experienced such higher exposures. Moreover, the importance of cumulative lead exposure with respect to such endpoints in adults is reinforced by the finding that bone lead concentration has been a stronger predictor of the effect than contemporaneous blood lead in studies where both biomarkers were available for analysis.

In light of this, the monograph might consider clarifying what is meant by use of terminology that states that there is "**sufficient evidence"** of an association between blood lead and various health endpoints in adults. For example, in section 1.4.4, page XIX, the monograph states, "The NTP concludes that there is sufficient evidence that blood Pb levels <10µg/dL in adults are associated with adverse effects on cardiovascular function." Later in that same paragraph, the monograph goes on to state, "*Chronic Pb exposure appears to be more critical than current Pb exposure as indicated by more consistent associations between chronic cardiovascular effects and bone Pb as compared to blood Pb. Studies support an association with concurrent blood Pb levels; however, the potential effect of early-life blood Pb levels on cardiovascular outcomes in adults cannot be discriminated from the effect of concurrent blood Pb levels without additional prospective studies in a population for which blood Pb levels remain consistently below 10µg/dL from birth until evaluation of the various cardiovascular outcomes*." Implicit in this reasoning is that the currently available evidence is <u>insufficient</u> to support a conclusion that the association between blood lead concentrations less than 10 µg/dL and these cardiovascular endpoints <u>is causal</u>. It would be helpful if this distinction with respect to **causality** were explicitly acknowledged in the monograph.

The same concerns apply to causal inference regarding blood lead concentrations less than 5 µg/dL and decrements in renal function. In this situation, causal inference is not only limited by consideration of the potential role of higher blood lead concentrations earlier in life. Because most lead is eliminated from the body by renal excretion, the contribution of <u>reverse causation</u> to the association of blood lead concentrations less

than 5 µg/dL and biomarkers such as serum creatinine or creatinine clearance or glomerular filtration rate should given adequate consideration. With all due respect, I think the current narrative in the NTP monograph is too dismissive of the potential role of reverse causation. At the top of page 97, the document states that the strongest evidence against reverse causality comes from the prospective study of Yu and colleagues in Taiwan published in 2004. In my opinion, this study is subject to multiple limitations that limit its ability to contribute to causal inference, not the least of which are issues concerning lack of blinding. Note that the nonblinded investigators who were studying the relationship between blood lead and renal function in these subjects with compromised renal function were also the same doctors who were treating and counseling the subjects with respect to diet and blood pressure, key factors that influence the progression of renal insufficiency. Unfortunately, this limitation, and many others, do not seem to be addressed in the narrative, or the tables that summarize key studies.

In the same paragraph at the top of page 97, the narrative notes that 2 publications from the Normative Aging Study observed associations between blood lead and serum creatinine “across the entire range of serum creatinine, including at levels in the normal range where [the narrative states] reverse causality would not be occurring”. No experimental basis or scientific rationale is offered for the inference that reverse causality could not be operative in the “normal range” of serum creatinine. On the contrary, the glomerular filtration rate within and between individuals varies considerably in the broad “normal range” of serum creatinine. In any person, decrements in glomerular filtration rate are associated with increases in serum creatinine even when the serum creatinine remains in the “normal range”. Finally, any conclusion that a casual relationship exists between blood lead concentrations as low as 2 µg/dL and decrements in renal function should be tempered by the lack of studies that have identified a nephrotoxic lesion or mechanism induced by a blood lead concentrations as low as 2 µg/dL in humans or experimental animals. On the contrary, early biomarkers of tubular damage have not been consistently observed in occupational cohorts or animal studies until blood lead concentrations are generally higher by an order of magnitude.

Overall, I think the document would be improved by explicitly highlighting and critically addressing key strengths and weaknesses in the studies that form the basis for associations between low-level lead exposure and multiple health endpoints. For example, with respect to low level lead exposure and ADHD, the narrative appropriately points out the association is strengthened by the fact that it has been observed in multiple epidemiological investigations, most of which have been cross-sectional or case-control studies. Unfortunately, the document apparently does not point out that virtually all of these studies were unable to control for parental ADHD, a key covariate that could readily confound the relationship. If both strengths and weaknesses are discussed and assessed, the document will greatly succeed in both informing public policy, and in encouraging ongoing research.